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Embedding Evolutionary Game Theory into an Optimal Control Framework for Drug Dosage Design

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Abstract— **In this paper, we show how evolutionary game theory can be embedded into a traditional optimal control framework in order to predict strategies for time-dependent drug dosages in the context of a growing pathogen population that exhibits the capacity to evolve in direct response to the level of applied drug. To illustrate our method for integrating evolutionary games with optimal control systems, we consider a simplified model that describes a generic trade-off between viral replication rate and drug resistance. The technique that we outline, however, is readily extendable to more complicated models that account, in more detail, for the specific biology of a particular pathogen of interest.**

I. Introduction

ONE of the primary challenges associated with treating an individual for a viral or bacterial disease is designing an effective and safe treatment scheme. Ideally, one would like to be able to predict the optimal medication dosage as a function of time so that the individual being treated is rapidly cured while at the same time suffers limited drug associated side-effects. Quantitative prediction of the best time-dependent scheme for drug dosages, of course, requires a mathematical framework like optimal control theory. While optimal control theory has, in the past, been used to suggest optimal drug dosages for particular diseases like HIV[1], these optimal control schemes typically assume that the pathogen remains passive and relatively unchanging.

More recently, Kutch and Gurfil[2] have considered the problem of optimal drug dosages in a continuously-mutating viral population. While their model captures the interplay between drugs and pathogens in a more realistic manner, it falls short of the true breadth of the viral response to the extent that it considers a single drug-resistant pool of HIV viruses, all sharing roughly similar dynamics. A more accurate description of infections, particularly those characterized by rapidly mutating pathogens like retroviruses, however, is a spectrum of viral strains, each having slightly different biological responses to the drug and also slightly different natural biology. All of these strains, of course, compete with one another for survival and replication into the next generation. The selective advantage associated with one strain over another, however, is crucially dependent on its environment and, more specifically, on the level and type of drug treatment that it is experiencing.

According to the competitive exclusion principle [3], strains which replicate more slowly in both drug and drug-free environments can never establish dominance within the host. As a result, the strains that need to be considered when analyzing the interplay between drugs and pathogen populations are only those strains that exhibit the largest replication rate for at least one drug concentration. On the other hand, trade-offs between drug-resistance and replication capacity have been well documented [4-7]. As a result, replacement of one pathogen strain by another may be triggered by changing levels of drug dosages.

The problem of competition for survival within a species has a long history in biological fields, starting with the seminal work of Darwin[8]. The mathematical framework for analyzing competition and evolution, however, appeared much later, primarily through the works of John Maynard Smith[9] who developed the theory of evolutionary games. More recently, evolutionary game theory has been extended and analyzed in several reviews[10, 11], and has found application to a wide array of different biological sciences[12], from rationalizing the emergence of particular behavioral phenotypes[13] to addressing questions regarding pathogen infectious strategies[14].

The mathematical framework of evolutionary games provides an obvious model structure for contemplating the interplay between pathogens and drugs, since it can be used to formally describe the competitive interactions that lead one pathogen strain to dominate and, ultimately, replace another pathogen strain as a result of varying drug treatments. To our knowledge, however, no one has integrated evolutionary game theory into the context of optimal control in order to predict time-dependent schemes for drug dosages. By embedding an evolutionary game into the viral dynamics associated with definition of an optimal drug treatment strategy, however, the predicted optimal control will naturally account for both viral population dynamics, and viral evolutionary dynamics (or Darwinian dynamics). As a result, the optimal control scheme will not only function in the face of viral evolution, but also, will use viral evolution to its advantage. In this paper, we consider a simplified model and show how several assumptions allow us to easily integrate evolutionary games into drug dosage optimal control formulations. The model that we use is chosen to be simple

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and illustrative; however the approach that we develop should be easily extended to more complicated, pathogen specific models that are of interest to the medical community.

II. Model Formulation

A. Viral Replication Dynamics

To model viral population dynamics, we consider basic logistic growth. Since, however, the model must specifically account for mutation and drug resistance, we additionally incorporate a parameter, u_m that describes the 'mutational distance' of a particular pathogen subpopulation from the wild-type (WT) strain. This allows us to define the following equation for viral population growth

$$\dot{v} = \left(g e^{\frac{-u_m^2}{w_r}} - s_d u_d e^{\frac{-u_m^2}{w_d}} \right) v \left(1 - \frac{v}{K} \right) \quad (1)$$

where g is the WT growth rate in the absence of drugs, K is the viral carrying capacity, u_d is the concentration of drugs in the system, s_d is a coefficient that describes the decrease in the rate of WT viral replication per unit drug and w_r and w_d are parameters that capture how rapidly viral replication and drug efficacy fall off as a function of mutational distance from the WT strain. For notational simplicity, time has been suppressed in equation (1), although v and u_d will exhibit time dependence. Notice that in this model, we simplify the mutation space of the real system by assuming a generic mutational distance. The assumption is that all strains that are competitive enough to establish at a specific drug dosage level exhibit a trade-off between replication capacity and drug resistance. While this has been documented in certain pathogen systems[4], the use of a single dimension to represent the state space of potential gene combinations is obviously an approximation. Additionally, we have assumed Gaussian functions to describe the dependence of both replication rates and drug resistance on mutational distance. In fact, even when projected onto one dimension, the use of Gaussian functions is somewhat of an oversimplification. Complicating factors include discontinuities that occur when no viable pathogen strains exist with intermediate ranges of replication rates and drug resistance, and the potential emergence of a mutant strain with both an increased replication rate and an increased drug resistance. For these scenarios, evolution over a discrete set of states must be considered, and is beyond the scope of the present work. Provided, however, that both drug resistance and replication rates are relatively smooth functions of the idealized mutational distance measure, the technique that we use is valid. In cases where replication rate and drug resistance are deemed to fall off differently, the Gaussian functions in equation (1) can be replaced by more suitable functional approximations for the landscape of viral properties.

B. Viral Competition through Evolutionary Game Theory

In traditional game theory, a payoff function is defined and players in the game are assumed to choose their strategies based on optimization of the payoff. For evolutionary games, the payoff is taken as the number of progeny that an organism playing by a particular strategy will contribute to the next generation. For our model of drug resistance, the pathogen strategy will be taken as mutational distance, u_m. This allows us to define a fitness generating function, or G-function, for each possible pathogen strategy, u_m'. From equation (1), the G-function can be extracted as the per virion replication rate for pathogens playing strategy u_m', thus

$$G(u_m', \bar{u}_m, v) = G\big|_{u_m'} = \left(g e^{\frac{-(u_m')^2}{w_r}} - s_d u_d e^{\frac{-(u_m')^2}{w_d}} \right) \left(1 - \frac{v}{K} \right) \quad (2)$$

In formulating equation (2) as the G-function, we have assumed that pathogen phenotypes congregate around some mean strategy value, $\bar{u}_m$. In order for one pathogen strain to replace another at the population level, the G-function for the invading strain (and thus the strain's relative fitness) must be greater than the G-function for the strain playing according to the average strategy value $\bar{u}_m$

$$G\big|_{u_m'} > G\big|_{\bar{u}_m} \quad (3)$$

In standard evolutionary games, the G-function for a particular invading strain can be written as an explicit function of the average strategy, $\bar{u}_m$. Equation (2), however, presents a slight twist on this typical formulation. More specifically, while the G-function *does* depend on the average composition of the pathogen population, this dependence is not through the average behavior of the population itself, but rather it is through u_d, the optimally selected drug dosage. As a result, G-function dependence on $\bar{u}_m$ does not evolve in real time as would be expected for a scenario where the dependence is directly correlated with a natural, internal parameter of the system (eg. strain effects on the carrying capacity). Rather, in equation (2) the dependence of G on $\bar{u}_m$ emerges through selection of the time-dependent drug regimen that is applied to optimally defend against the pathogen population. Because u_d is an externally applied condition determined by rational medical professionals, it should, at least in theory, be selected based not only on the *current state* of the system, but also on the *projected future state* of the system. In the current framework, where the goal is, itself, to predict the best drug treatment strategy u_d as a function of time, we use optimal control over a time window T to relate u_d in equation (2) to the state of the pathogen population and, in particular, to the average mutational distances $\bar{u}_m$ that dominates in the community over the drug treatment period. For all of the simulations in this paper, the time window is set arbitrarily at $T = 1$, however in a clinical setting, T would be chosen as the desired length of the

treatment period for a particular patient. In what follows, we show how both u_d and the evolutionary game can be solved for simultaneously by embedding the game theoretic treatment of viral competition into an optimal control framework through Darwinian Dynamics.

C. Darwinian Dynamics for Strategy Evolution

To develop an expression describing the time evolution of the population wide average pathogen strategy, $\bar{u}_m$, we begin by defining the average strategy in terms of population composition. To do this, we express the sizes of the pathogen subpopulations as a function of pathogen strategy, $v(u_m)$. The average pathogen strategy can then be found as

$$\bar{u}_m = \frac{\int_0^\infty u_m v(u_m) du_m}{\int_0^\infty v(u_m) du_m} = \frac{\int_0^\infty u_m v(u_m) du_m}{v_T} \tag{4}$$

We then take the derivative of equation (4) assuming that the strategies themselves do not change in time, but rather, that there are a fixed set of available strategies which may be more or less populated depending on the selective forces acting on the pathogen population at any given point in time. This gives

$$\begin{aligned} \dot{\bar{u}}_m &= \frac{\int_0^\infty u_m \left\{ \dot{v}(u_m) v_T - \dot{v}_T v(u_m) \right\} du_m}{v_T^2} \\ &= \int_0^\infty \left\{ u_m \frac{v(u_m)}{v_T} \left[G\big|_{u_m} - G\big|_{\bar{u}_m} \right] \right\} du_m \end{aligned} \tag{5}$$

where we have used equations (1) and (2) to arrive at the second equality above. Equation (5) can be approximated by expressing the G-function term according to a first order Taylor expansion. This gives

$$\dot{\bar{u}}_m = \int_0^\infty \left\{ u_m \frac{v(u_m)}{v_T} \frac{\partial G}{\partial u}\bigg|_{\bar{u}_m} \delta u_m \right\} du_m = \sigma^2 \frac{\partial G}{\partial u}\bigg|_{\bar{u}_m} \tag{6}$$

where

$$\frac{\partial G}{\partial u}\bigg|_{\bar{u}_m} = \frac{\partial G(u, \bar{u}_m, v)}{\partial u}\bigg|_{u=\bar{u}_m}, \quad \delta u_m = u_m - \bar{u}_m \quad \text{and}$$

$$\sigma^2 = \int_0^\infty \left\{ u_m \frac{v(u_m)}{v_T} \delta u_m \right\} du_m \tag{7}$$

The derivation of Darwinian Dynamics presented above follows closely the approach taken by Vincent and Brown in [10]. The term σ^2 is reflective of the overall rate of evolutionary change. While σ^2 could, technically, be calculated based on a specific model for viral growth, in reality, this term should capture additional complexities associated with strategy dynamics (see [10]). As a result, it is often better to treat σ^2 as a model parameter.

D. Optimal Control for Drug Dosage Design

The ultimate goal of this paper is to propose a formulation for predicting optimal time-dependent drug dosages in the context of a growing pathogen population that shifts according to intra-population competitive interactions in response to the drug dosage itself. To that end, we now turn to the task of defining the optimal control problem. In general, when considering optimal drug strategies, optimality is defined as some trade-off between reducing the pathogen load, and minimizing drug dosages, thus we define the optimal control problem as

$$J = \min_{u_d} \left\{ \alpha v(T) + \int_0^T \left(v^2 + \beta u_d^2 \right) dt \right\} \tag{8.a}$$

subject to

$$v(0) = v_0 \ , \ \ \bar{u}_m(0) = \bar{u}_{m,0} \tag{8.b}$$

$$0 \le u_d \le u_{d,\max} \tag{8.c}$$

$$\dot{\bar{u}}_m = \sigma^2 \left(-\frac{2\bar{u}_m g e^{\frac{-(\bar{u}_m)^2}{w_r}}}{w_r} + \frac{2\bar{u}_m s_d u_d e^{\frac{-(\bar{u}_m)^2}{w_d}}}{w_d} \right) \left(1 - \frac{v}{K} \right) \tag{8.d}$$

$$\dot{v} = \left(g e^{\frac{-\bar{u}_m^2}{w_r}} - s_d u_d e^{\frac{-\bar{u}_m^2}{w_d}} \right) v \left(1 - \frac{v}{K} \right) \tag{8.e}$$

where equation (8.d) can be derived from equations (2) and (6), while equation (8.e) is equation (1) evaluated at the average pathogen strategy value, $\bar{u}_m$. Notice that $\bar{u}_m$ in equation (8.e) is now a function of time, since the average pathogen strategy shifts in response to the drug treatment. In equation (8.a), the parameter β reflects the cost of high drug dosages relative to high pathogen loads, and should be chosen to reflect not only the monetary costs associated with the drug, but also the health costs including risk of damage to organs, risk of death, etc. The other parameter in equation (8.a), α, reflects the relative cost of having a high pathogen load at the end of the treatment and should be chosen to bring the pathogen population to within acceptable levels over the treatment period, T.

III. Results and Discussion

To solve the optimal control problem in equation (8), we use the Pontryagin Maximum Principle. More specifically, we define the Hamiltonian for the system as

$$H = v^2 + \beta u_d^2 + \lambda_u \dot{\bar{u}}_m + \lambda_v \dot{v} \tag{9}$$

where λ_u and λ_v are costate variables for v and $\bar{u}_m$ respectively. We then define the adjoint equations from the Hamiltonian according to the relationships $\dot{\lambda}_u = -\partial H / \partial \bar{u}_m$ and $\dot{\lambda}_v = -\partial H / \partial v$. Last, we find an expression for the optimal control, u_d, by solving the equation $\partial H / \partial u_d = 0$. This gives

$$u_d = \frac{\frac{e^{-\bar{u}_m^2/w_d}}{w_d} s_d \left(\lambda_v v w_d - 2\lambda_u \sigma^2 \bar{u}_m\right)(K - v)}{2\beta w_d K} \quad (10)$$

which can be substituted back into both equations (8.d) and (8.e) and the adjoint equations. We thereby arrive at a set of four coupled ordinary differential equations which, together with the initial conditions in equation (8.b), and the final conditions $\lambda_u(T) = 0$ and $\lambda_v(T) = \alpha$, completely define the optimal control system. In what follows, we use a backward-forward sweep algorithm that integrates the state variables forward in time and the costate variables backward in time iteratively until the solution has converged. Figure 1 shows the results of a simulation for $g = 100$, $s_d = 1$, $K = 10000$, $v_0 = 2000$, $\bar{u}_m(0) = 0.001$, $\alpha = 10000$, $\sigma = 5$ and various values of w_r, w_d and β.

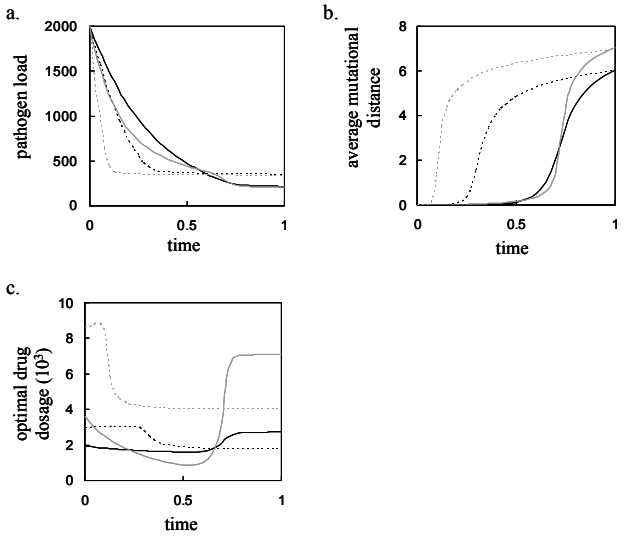

Figure 1 (a) pathogen load, (b) average 'mutational distance' and (c) optimal drug dosage. The parameters used are $g = 100$, $s_d = 1$, $K = 10000$, $v_0 = 2000$, $\bar{u}_m(0) = 0.001$, $\alpha = 10000$, $\sigma = 5$, $\beta = 1$ (grey lines), $\beta = 10$ (black lines), $w_r = 8$, $w_d = 10$ (solid) and $w_r = 10$, $w_d = 8$ (dotted).

From these simulations, we see several trends. First, optimal drug dosages vary more significantly through time when the cost associated with drug application is higher. Similarly, lower costs result in a significantly higher level of drug application overall, as would be expected. Another, less intuitive trend, however, is the observation that when pathogen replication rates fall off more rapidly than drug resistance with mutation, the optimal drug strategy is to limit drug application during the first half of the treatment phase, and then to increase the drug load over the second half of the treatment phase. In contrast, when pathogen replication rates fall off less rapidly than drug resistance with mutation the optimal drug strategy is to use high drug dosages during the early phase of the treatment regime, and then to drop the drug dosages as the treatment process proceeds.

IV. Conclusions

In this paper, we have shown how an evolutionary game describing competitive interactions within a pathogen population can be embedded into an optimal control framework for predicting drug dosage strategies. Though this technique was presented for a very generic model of pathogen population dynamics in the presence of an applied drug, the method can easily be extended to more complicated models, or models that are developed to specifically describe the population dynamics of a particular pathogen population. By embedding game theory into the standard optimal control framework, we naturally consider pathogen evolution in devising the optimal control strategy. As a result, drug dosages are selected to best defend against a pathogen invader not only in the face of pathogen population growth, but also in the context of pathogen mutation that drives pathogen evolution in response to the drug treatment strategy. Given that our optimal control framework explicitly accounts for the actions of drugs on pathogen population composition, we suggest that this novel integration of evolutionary game theory and optimal control will prove particularly useful in devising treatment strategies for pathogens, including retroviruses like HIV, that are characterized by rapid mutation rates and the frequent emergence of drug resistant strains.

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